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# Anticoagulation After Stroke in Patients With Atrial Fibrillation To Bridge or Not With Low-Molecular-Weight Heparin?

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**Background and Purpose**—Bridging therapy with low-molecular-weight heparin reportedly leads to a worse outcome for acute cardioembolic stroke patients because of a higher incidence of intracerebral bleeding. However, this practice is common in clinical settings. This observational study aimed to compare (1) the clinical profiles of patients receiving and not receiving bridging therapy, (2) overall group outcomes, and (3) outcomes according to the type of anticoagulant prescribed.

**Methods**—We analyzed data of patients from the prospective RAF and RAF-NOACs studies. The primary outcome was defined as the composite of ischemic stroke, transient ischemic attack, systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding observed at 90 days after the acute stroke.

**Results**—Of 1810 patients who initiated oral anticoagulant therapy, 371 (20%) underwent bridging therapy with full-dose low-molecular-weight heparin. Older age and the presence of leukoaraiosis were inversely correlated with the use of bridging therapy. Forty-two bridged patients (11.3%) reached the combined outcome versus 72 (5.0%) of the nonbridged patients ( $P=0.0001$ ). At multivariable analysis, bridging therapy was associated with the composite end point (odds ratio, 2.3; 95% CI, 1.4–3.7;  $P<0.0001$ ), as well as ischemic (odds ratio, 2.2; 95% CI, 1.3–3.9;  $P=0.005$ ) and hemorrhagic (odds ratio, 2.4; 95% CI, 1.2–4.9;  $P=0.01$ ) end points separately.

**Conclusions**—Our findings suggest that patients receiving low-molecular-weight heparin have a higher risk of early ischemic recurrence and hemorrhagic transformation compared with nonbridged patients. (*Stroke*. 2019;50:2093–2100. DOI: 10.1161/STROKEAHA.118.022856.)

**Key Words:** anticoagulants ■ atrial fibrillation ■ humans ■ incidence ■ secondary prevention

#### See related article, p 1950

Oral anticoagulant therapy (OAC) is the treatment of choice for secondary prevention of stroke in patients with nonvalvular atrial fibrillation (AF). For this indication, the currently approved OACs are vitamin K antagonists (VKAs) and non-VKA oral anticoagulants (NOACs). VKAs are slower than NOACs in reaching the therapeutic anticoagulant effect, as their mechanism of action is the inhibition of vitamin K–dependent coagulation factors, which requires few days. The effect of VKAs is measured through the international normalized ratio that, as reflects the activity of VKA, requires few days to reach the therapeutic target. In some cases, a temporary therapy with full-dose low-molecular-weight heparin (LMWH) can be given alongside warfarin until the therapeutic international normalized ratio level is achieved. Moreover, bridging therapy is used to counteract the transient prothrombotic effect in the initial phase of OAC treatment.<sup>1</sup>

The advantages of NOACs are their rapidity of action (2–3 hours for dabigatran, 2–4 hours for rivaroxaban, 3–4 hours for apixaban, and 1–2 hours for edoxaban) and fast reversal,

similar to heparin in that respect. Moreover, their standard dosages do not require titration, whereas VKAs do.

Despite evidence that full-dose LMWH can be harmful in acute stroke care<sup>2</sup> in particular in the presence of AF,<sup>3</sup> there are anecdotal reports of its use in selected patients.<sup>4,5</sup> Mostly, acute heparin treatment is used as bridging therapy until the therapeutic range of OACs is achieved—the so-called bridging therapy.<sup>1</sup>

By using data from the prospective RAF<sup>6</sup> and RAF-NOACs<sup>7</sup> studies, we aimed to evaluate (1) the clinical profiles of patients who received or not bridging therapy, (2) differences in outcomes between these 2 groups, and (3) differences in outcomes according to the type of OAC prescribed.

#### Patients and Methods

We analyzed the data of patients from the prospective RAF (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation) and RAF-NOACs (Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants) studies that

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enrolled consecutive patients with acute ischemic stroke and nonvalvular AF. The methods and results of the RAF studies have been previously described in detail,<sup>6,7</sup> and the data are available from the corresponding author on reasonable request. Both studies were approved by the local institutional review board if required. Patient exclusion criteria for both studies were high risk of bleeding, defined as clinically significant liver disease (acute or chronic hepatitis, cirrhosis, or alanine aminotransferase level  $>3\times$  the upper limit of normality), creatinine clearance  $<30$  mL/min (for apixaban, the threshold was 25 mL/min), life expectancy of  $<3$  to 6 months, the presence of uncontrolled hypertension,<sup>8</sup> and the ongoing prescription of medications having known metabolic interactions with any type of OACs.

A noncontrast cerebral computed tomography (CT) or cerebral magnetic resonance scan was performed on admission for each patient, to exclude for the presence of intracranial hemorrhage. Thrombolysis treatment was administered according to standard protocol, when appropriate. All of the participating centers provided stroke unit care according to current international recommendations for acute ischemic stroke treatment.<sup>9,10</sup> Stroke physicians were free to make decisions on the type of anticoagulant to be used for secondary prevention, as well as its starting time.

Nonvalvular AF was classified as paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting  $>7$  days requiring pharmacological or electrical stimulation), or permanent (persisting for  $>1$  year, either because cardioversion failed or had not been attempted).<sup>11</sup>

A second brain CT scan or magnetic resonance was performed 24 to 72 hours from stroke onset for all patients. Hemorrhagic transformation (HT) was defined on CT scan as any degree of hyperdensity within the area of low attenuation and was classified as either hemorrhagic infarction or parenchymal hematoma.<sup>12,13</sup> On magnetic resonance imaging, HT was defined as hypointensity on axial T1-weighted or T2-weighted images. HT was considered to be symptomatic if it was associated with an increase of  $\geq 4$  points in the National Institutes of Health Stroke Scale (NIHSS), score and there was no evidence of intracranial bleeding on the first CT.<sup>14</sup> The sites and sizes of the qualifying infarcts were determined based on standard templates<sup>15,16</sup> as (1) small, when a lesion was  $\leq 1.5$  cm in the anterior or posterior circulation; (2) medium, when a lesion was in a superficial cortical branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, in a cortical superficial branch of the anterior cerebral artery; (3) large anterior, when a lesion involved the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in 2 superficial cortical branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in  $>1$  artery territory (eg, MCA associated to anterior cerebral artery territories); and (4) large posterior, when a lesion was  $\geq 1.5$  cm in the brain stem or cerebellum.<sup>13</sup>

For the purpose of this analysis, bridging therapy was defined as any temporary full dose of LMWH (eg, 100 UI/kg of enoxaparin twice a day) started together before or with VKAs, to cover the time needed by the latter to reach the therapeutic

effect<sup>1</sup> or as any full dose (given for at least 24 hours) of LMWH before the use of an NOAC.

## Risk Factors

Data on stroke risk factors were collected as described previously<sup>6,7</sup>: age, sex, history of hypertension (blood pressure of  $\geq 140/90$  mmHg at least twice before stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting serum glucose level  $\geq 126$  mg/dL preprandial on 2 examinations, glucose level  $\geq 200$  mg/dL postprandial, or glycated haemoglobin  $\geq 6.5\%$ , or under antidiabetic treatment), current cigarette smoking, past smoking (cessation  $<5$  years ago), hyperlipidemia (total cholesterol  $\geq 200$  mg/dL or triglyceride  $\geq 140$  mg/dL or already under lipid-lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral artery disease (intermittent claudication of presumed atherosclerotic origin or ankle/arm systolic blood pressure ratio  $<0.85$  in either leg at rest or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse ( $\geq 300$  g per week), obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), or previous stroke/transient ischemic attack (TIA) White matter changes (leukoaraiosis) defined on the first CT (or magnetic resonance imaging) examination as ill defined and moderately hypodense (or hyperintensity on T2 weighted on magnetic resonance imaging) areas of  $\geq 5$  mm according to published criteria were investigated.<sup>17</sup> Leukoaraiosis in the deep white matter was dichotomized into absent versus mild, moderate, or severe. Other baseline variables obtained at admission for all patients included fasting serum glucose, fasting serum cholesterol (total, HDL [high-density lipoprotein], and LDL [low-density lipoprotein]), platelet count, international normalized ratios, activated partial thromboplastin time, systolic blood pressure, and diastolic blood pressure.

Data on the use of any antiplatelet, anticoagulants, or thrombolytic agent, before admission, at baseline, and during the follow-up period, were recorded.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was calculated before and after the index event.<sup>18</sup>

## Evaluation of Outcomes

Patients were followed up prospectively through face-to-face or telephone interviews. Study outcomes at 90 days were (1) recurrent ischemic cerebrovascular events (stroke or TIA) or symptomatic systemic embolisms; (2) symptomatic cerebral bleedings or major extracerebral bleedings.

The primary study outcome was the composite of stroke, TIA, systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding.<sup>6,7</sup> HTs found on neuroimaging 24 to 72 hours after onset were not considered outcome events unless classified as symptomatic.

Stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and categorized as ischemic or hemorrhagic. TIA was defined as a



transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy. Cerebral bleeding was considered symptomatic if associated with a decline in neurological status (an increase of  $\geq 4$  points in the NIHSS score or leading to death). Major extracerebral bleeding was defined as a reduction in the hemoglobin level of at least 2 g/dL, requiring blood transfusion of at least 2 units, or symptomatic bleeding in a critical area or organ.<sup>19</sup>

Disability and mortality at 90 days were also assessed using the modified Rankin Scale. Nondisabling functional outcome was defined as an modified Rankin Scale score of 0 to 2.

### Statistical Analysis

Differences in patient characteristics between the 2 groups (bridging versus nonbridging therapy) were assessed utilizing the  $\chi^2$  test. Univariable analysis was performed to compare clinical features at admission and their risk factors. The 2 continuous variables, NIHSS score and age, are reported as mean values and SDs, whereas categorical variables are reported as percentages.

Multivariable logistic regression was performed to investigate independent variables and their possible correlations with the bridging therapy. The variables included in the model were NIHSS score, the presence of diabetes mellitus, arterial hypertension, dyslipidemia, paroxysmal AF, pacemaker; lesion size, leukoaraiosis, CHA<sub>2</sub>DS<sub>2</sub>-VASc score after the event, as well as the histories of stroke or TIA, current smoking habit, congestive heart failure, and myocardial infarction.

Univariable analysis was used to compare the combined outcomes of the 2 groups, for recurrence of ischemic stroke and occurrence of bleeding. The same analysis was performed to compare the combined outcomes of the 2 OAC regimens.

Given the difference of numbers of patients in the 2 groups, and the possible presence of confounding factors influencing outcomes, a propensity score (PS) matching was also performed, and outcomes were evaluated in the 2 groups, each of 323 patients, obtained after matching<sup>20</sup>; the PS is the probability that a patient would have been treated with bridging therapy with LMWH given his pretreatment variables. Equal PS values guarantee equal distribution of measured pretreatment variables at baseline on the sample level; thus, PS is an attempt to create homogeneous groups for comparison when data from a randomization procedure are not available. The individual PSs for analyzing bridging and nonbridging therapy groups were estimated with a logit model including the following variables: age, sex, NIHSS at admission, vascular risk factors, lesion size, use of NOACs, and CHA<sub>2</sub>DS<sub>2</sub>-VASc. To estimate treatment effects, Cox proportional hazards models were performed on the entire cohort to derive crude and PS-adjusted hazard ratios (HRs).

The observed correlation between the combined outcome (survival) and the set of variables was analyzed using the proportional Cox model; here, all the variables included in our

multivariable analysis were used. Patients were censored at the time of an outcome event, death, or lost during follow-up.

### Results

A total of 2164 patients were enrolled in the RAF (n=1037) and RAF-NOACs (n=1127) studies. Patients who did not start any anticoagulation were excluded, as well as those who were treated only with LMWH. This resulted in 1821 patients, of whom another 11 were excluded because of incomplete data related to the administration of OAC therapy. A further 30 patients were lost during follow-up.

After index acute ischemic stroke, 371 of 1810 patients (20.49%) underwent bridging therapy with LMWH (Figure 1 in the [online-only Data Supplement](#)).

OAC was initiated with warfarin in 561 of 1780 patients (31.52%), and NOACs were started in 1219 of 1780 (68.48%). The median for initiating bridging therapy was 7 days (interquartile range, 11), whereas for the nonbridging group, this number was a median of 8 days (interquartile range, 14). Mean NIHSS at admission was  $7.2 \pm 6.3$  in the bridging group and  $7.7 \pm 6.2$  in the nonbridging group ( $P=NS$ ).

**Table 1. Clinical Characteristics of Study Patients (n=1810)**

Clinical Characteristics of Patients (n=1810)	Bridging Therapy (n=371)	Nonbridging Therapy (n=1439)	P Value
Age, y	73.0 $\pm$ 9.7	76.1 $\pm$ 9.4	0.0001
Male sex	197 (53.1%)	663 (46.1%)	0.017
NIHSS at admission	7.2 $\pm$ 6.3	7.7 $\pm$ 6.2	NS
Diabetes mellitus	80 (21.6%)	297 (20.6%)	NS
Hypertension	275 (74.1%)	1124 (78.1%)	NS
Dyslipidemia	118 (31.8%)	510 (35.4%)	NS
Paroxysmal AF	153 (41.2%)	656 (45.6%)	NS
Smoking habit	46 (12.4%)	140 (9.7%)	NS
History of stroke/TIA	84 (22.6%)	382 (26.5%)	NS
History of CHF	74 (19.9%)	232 (16.0%)	NS
History of MI	48 (12.9%)	183 (12.7%)	NS
History of PAD	40 (10.8%)	116 (8.1%)	NS
PMK	21 (5.7%)	93 (6.5%)	NS
HT, 24–72 h	40 (10.8%)	135 (9.4%)	NS
Poststroke CHA <sub>2</sub> DS <sub>2</sub> -VASc $>4$	255 (68.7%)	1094 (76.0%)	0.03
Antiplatelet therapy	41 (11.0%)	200 (13.9%)	NS
Cerebral infarct pattern			
Small	153 (41.2%)	582 (40.4%)	NS
Medium	153 (41.2%)	469 (32.6%)	0.010
Large anterior circulation	41 (11.1%)	232 (16.1%)	0.006
Large posterior circulation	15 (4.0%)	92 (6.4%)	NS
Leukoaraiosis	143 (38.5%)	786 (54.6%)	0.0001

AF indicates atrial fibrillation; CHF, congestive heart failure; HT, hemorrhagic transformation; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NS, nonsignificant; PAD, peripheral artery disease; PMK, pacemaker; and TIA, transient ischemic attack.

## Clinical Characteristics of the Bridging and Nonbridging Groups

The bridging and nonbridging groups differed for age, sex, the percentage of medium-sized lesions, of large anterior circulation lesions, and for the presence of leukoaraiosis (Table 1). The mean ages were  $73.0 \pm 9.7$  versus  $76.1 \pm 9.4$  years, respectively ( $P < 0.001$ ). Of the 371 bridging patients, 197 (53.1%) were male, versus 663 males (46.1%) in the nonbridging group ( $P = 0.017$ ). In the bridging group, 153 patients (41.2%) had medium-sized lesions versus 469 (32.6%) in the nonbridging group ( $P = 0.010$ ); large anterior lesions were present in 41 (11.1%) of bridging patients and 232 (16.1%) nonbridging patients ( $P = 0.006$ ). Leukoaraiosis was diagnosed in 143 (38.5%) and 786 (54.6%) patients, respectively ( $P = 0.001$ ).

Forty-one of 371 (11.0%) in the bridging group were simultaneously taking an antiplatelet agent (either aspirin, 100 mg per day, or clopidogrel, 75 mg per day), whereas in the nonbridging group, patients under antiplatelet therapy were 200 of 1439 (13.9%), being statistically similar ( $P = 0.2$ ).

At multivariable analysis, age (odds ratio [OR], 0.97; 95% CI, 0.95–0.98;  $P = 0.001$ ) and leukoaraiosis (OR, 0.60; 95% CI, 0.47–0.78;  $P = 0.001$ ) were inversely correlated with the use of bridging therapy (Table I in the [online-only Data Supplement](#)).

## Outcomes in the Bridging and Nonbridging Groups

Overall, 42 of 371 bridging patients (11.3%) experienced the combined outcome, compared with 72 of 1409 in the nonbridged group (5.1%;  $P = 0.0001$ ). Within the bridging group, 29 of 42 (69%, 7.8% of all outcomes) versus 44 of 72 (61.1%, 3.1% of all outcomes) in the nonbridging group had an ischemic stroke, respectively. Major bleedings occurred in 19 of 42 patients (45.23%, 5.1% of all outcomes) in the bridging group and 32 of 72 (44.44%, 2.3% of all outcomes) in the nonbridging group ( $P = 0.08$ ; Table 2).

In the multivariable analysis, bridging therapy was associated with combined outcome (OR, 2.3; 95% CI, 1.4–3.7;  $P < 0.0001$ ), ischemic event (OR, 2.2; 95% CI, 1.3–3.9;  $P = 0.005$ ), and hemorrhagic event (OR, 2.4; 95% CI, 1.2–4.9;  $P = 0.01$ ; Table 3).

PS matching was performed on 323 patients in each group. The 2 groups were comparable for age ( $74.3 \pm 8.7$  years in the nonbridging group versus  $74.0 \pm 8.5$  years in the bridging group;  $P = 0.7$ ), sex (170 men, 52.6% of the total, in the nonbridging group versus 161 males, 49.8% of the total, in the bridging group;  $P = 0.5$ ), and NIHSS at admission ( $7.5 \pm 6.3$  versus  $7.6 \pm 6.3$ ); also, they were comparable for clinical characteristics; NOACs were used as anticoagulants in 114 patients (35.3%) in the nonbridging group versus 115 patients

**Table 2. Univariable Analysis: Differences in Outcomes at 90 Days Between Patients Treated With Bridging With Low-Molecular-Weight Heparin and Those Without Bridging Therapy**

Univariable Analysis (n=1780)	Bridging Therapy (n=371)	Nonbridging Therapy (n=1409)	P Value
Combined outcome	42 (11.3%)	72 (5.1%)	0.0001
Ischemic outcome	29 (7.8%)	44 (3.1%)	0.0001
Hemorrhagic outcome	19 (5.1%)	32 (2.3%)	0.008

**Table 3. Multivariable Analysis**

Logistic Regression Analysis		
	OR (95% CI)	P Value
Bridging therapy (combined outcome)	2.3 (1.4–3.7)	<0.0001
Bridging therapy (ischemic outcome)	2.2 (1.3–3.9)	0.005
Bridging therapy (hemorrhagic outcome)	2.4 (1.2–4.9)	0.01

Adjusted for NIHSS score, diabetes mellitus, arterial hypertension, dyslipidemia, paroxysmal AF, pacemaker; lesion size, leukoaraiosis, CHA<sub>2</sub>DS<sub>2</sub>-VASc score after the event, history of stroke or TIA, type of oral anticoagulant (VKA vs NOAC), current smoking, congestive heart failure, and myocardial infarction; differences in outcomes at 90 d between patients treated with bridging with LMWH and those without bridging therapy. AF indicates atrial fibrillation; LMWH, low-molecular-weight heparin; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; and VKA, vitamin K antagonist.

(35.6%) in the bridging group ( $P = 1.0$ ; Table II in the [online-only Data Supplement](#)).

The PS analysis confirmed the results of the multivariable analysis; bridging therapy was associated with combined outcome (HR, 3.08; 95% CI, 1.68–5.64;  $P < 0.001$ ), ischemic event (HR, 4.50; 95% CI, 1.88–10.75;  $P < 0.003$ ), and hemorrhagic event (HR, 2.71; 95% CI, 1.16–6.37;  $P = 0.017$ ; Table 4); the same results were confirmed after the PS was adjusted for age, sex, NIHSS at admission, vascular risk factors, lesion size, and CHA<sub>2</sub>DS<sub>2</sub>-VASc: combined outcome had an HR of 2.23 (95% CI, 1.41–3.52;  $P < 0.001$ ), ischemic event, an HR of 2.23 (95% CI, 1.29–3.88;  $P < 0.003$ ), and hemorrhagic event, an HR of 2.24 (95% CI, 1.15–4.36;  $P = 0.017$ ; Table 4).

In Figure II in the [online-only Data Supplement](#), the cumulative hazard rates for the combined outcome, in respect to treatment group, according to the Cox regression model (HR, 0.95; 95% CI, 0.60–1.49;  $P = 0.8$ ) are reported.

## Outcomes According to the Type of OAC Used in the Bridging and Nonbridging Groups

Of the 1780 included patients, 1219 were treated with NOACs and 561 with VKAs. The combined outcome was observed in

**Table 4. PS Matching: Outcomes**

	No Bridging Therapy (n=323)	Bridging Therapy (n=323)	HR (95% CI)	P Value
Combined outcome	13 (4.0%)	40 (12.3%)	Unadjusted, 3.08 (95% CI, 1.68–5.64)	0.0001
			Adjusted, 2.23 (95% CI, 1.41–3.52)	0.0001
Ischemic outcome	6 (1.9%)	27 (8.3%)	Unadjusted, 4.50 (95% CI, 1.88–10.75)	0.003
			Adjusted, 2.23 (95% CI, 1.29–3.88)	0.003
Hemorrhagic outcome	7 (2.2%)	19 (5.9%)	Unadjusted, 2.71 (95% CI, 1.16–6.37)	0.017
			Adjusted, 2.24 (95% CI, 1.15–4.36)	0.017

HR indicates hazard ratio; and PS, propensity score.

62 (5.1%) and 52 (9.3%) patients, respectively ( $P=0.01$ ). An ischemic outcome was observed in 35 (2.9%) and 38 (6.8%) of the patients treated with NOACs or VKA, respectively ( $P=0.0001$ ). The NOAC and VKA groups did not differ concerning the hemorrhagic events that were 29 (2.4%) and 22 (3.9%), respectively.

In the bridging group, 120 patients were treated with NOACs and 251 with VKAs; in the nonbridging group, 1099 patients were treated with NOACs and 310 with VKAs. Within each group, no statistically significant differences were observed in either the combined outcome or the hemorrhagic event rate according to the type of OAC used. However, a statistically significant difference was observed for the rate of ischemic events in the nonbridging group: 27 events (2.5%) in patients treated with NOACs versus 17 events (5.5%) in patients treated with VKAs ( $P=0.015$ ).

When stratifying each group according to the type of OAC, no statistically significant differences were observed between and within each group in outcome rates.

## Discussion

This combined analysis of the RAF and RAF-NOACs data suggested that bridging therapy was associated with overall higher risks of early ischemic recurrence and symptomatic intracranial bleeding, independently of the type of OACs administered. The latter finding is in line with that reported by IST (International Stroke Trial),<sup>21</sup> where an increase in hemorrhagic stroke was reported (1.2% for heparin versus 0.4% for aspirin). In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, incidence of myocardial infarction, stroke or systemic embolism, major bleeding, hospitalization, or death within 30 days was also significantly higher in patients receiving bridging therapy (13% versus 6.3%; adjusted OR, 1.94;  $P=0.0001$ ).<sup>22</sup>

Bridging therapy with heparin is sometimes started in subacute ischemic stroke, as it is thought to reduce the risk of ischemic recurrence because of a possible prothrombotic activity of warfarin at treatment initiation.<sup>23</sup> However, reliable data on warfarin's role in blocking endogenous anticoagulants have yet to be proven. It is plausible that warfarin alone might be more effective than bridging therapy with warfarin in the subacute phase of AF-associated stroke.

Another possible explanation of the increased ischemic stroke risk of heparin may be its underdosing as patient body weights are generally based on estimation. Moreover, our study did not allow to distinguish between ischemic recurrence in a different vascular territory from the index stroke, and recurrence in the same vascular territory, that may have been a progression of the first ischemia.<sup>24</sup>

In our study, bridging therapy with NOACs was also associated with a higher rate of ischemic events compared with those receiving NOACs alone. Besides RAF-NOAC, there are only a few prospective data available from observational studies on the safety and efficacy of early secondary prevention using NOACs after cardioembolic stroke. Of these, the SAMURAI-NVAF study (Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-NVAF) reported that no intracerebral hemorrhage was recorded after

an NOAC initiation within a median of 4 days poststroke,<sup>25</sup> whereas another observational study reported no significant difference in the rate of recurrent ischemic events when comparing early NOAC treatment within 7 days and after 7 days.<sup>26</sup> Ongoing studies such as the Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation<sup>27</sup> and the ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation Study<sup>28</sup>) are designed to estimate the benefit of early versus late initiation of NOACs in patients with acute ischemic stroke related to AF without bridging therapy. Regarding the use of antiplatelets before initiating oral anticoagulation, 11.0% of bridging and 13.9% of nonbridging patients had been prescribed aspirin or clopidogrel. Therefore, it does not seem plausible that the associations would significantly increase bleeding risks in patients treated with LMWH.

When comparing bridging versus nonbridging outcomes associated with OAC type, the risk profile associated with bridging appeared similar between NOACs and VKAs, therein suggesting that bridging therapy should be avoided particularly in patients who will be treated with NOACs in secondary prevention (see Cox regression survival curve, Figure II in the [online-only Data Supplement](#)).

An analysis of the patient profiles indicated that older patients (mean age, 76.1 versus 73.0 years), those with leukoaraiosis or with large anterior circulation lesions, were less likely to receive bridging therapy. This might reflect a routine use of LMWH in only selected cases, since leukoaraiosis and large infarct volume are clinical predictors of both symptomatic and asymptomatic HT,<sup>29–31</sup> both spontaneous<sup>29</sup> and after thrombolytic therapy.<sup>32</sup>

However, based on our study results, there seems to be still overuse of LMWH because of a nonadherence to current guidelines. This overuse may also be because of the slower reversal of VKA and to the absence, at the time of enrollment of the RAF and RAF-NOACs, of an antidote for NOACs in case of bleeding.<sup>33</sup> Regarding the choice of patients to be treated with bridging therapy, there could have been a selection bias. Moreover, unrecorded factor that can sway clinician decisions on the use of bridging therapy may include dysphagia in acute stroke phase, preferring subcutaneous-to-oral administrations.

A limitation of this analysis was that it was nonrandomized; so it is possible that some confounding factors might have influenced the outcome results. We did not have information on the exact time when international normalized ratio reached the target level in warfarin-treated patients. Moreover, the sizes of the 2 groups were not equally represented because only 20.5% of patients underwent bridging therapy with LMWH. Moreover, we are unable to specify the types of bleedings because the RAF and RAF-NOACs studies were not designed to collect such data.

In conclusion, our study suggests that the use of full-dose LMWH preceding oral anticoagulation in nonvalvular AF patients hospitalized for a recent ischemic stroke was associated with a higher risk of early ischemic recurrence and hemorrhagic events.

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